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CASE REPORT

Complete remission of primary hepatic lymphoma in a patient with human immunodeficiency virus

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Abstract

Diffuse large B cell primary hepatic lymphoma is a rare disease with limited available information regarding treatment strategy. Although the liver contains lymphoid tissue and is an important site for lymphocytes activation, primary hepatic lymphoma is rare. Host factors make the liver a poor environment for malignant lymphoma development. Its coexistence with human immunodeficiency virus (HIV) infection increases morbidity and mortality risks. Additionally, jaundice increases chances of developing adverse effects from chemotherapy. Here, we report a case of diffuse large B cell primary hepatic lymphoma in a 32-year-old HIV positive man. Due to elevated liver enzyme levels and jaundice, the patient was initially treated with an R-DHAP regimen, which was replaced with an R-CHOP regimen. Restaging images with a positron emission tomography scan after the latest chemotherapy cycle confirmed remission. This is the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature.

Key words: Primary hepatic lymphoma; Diffuse B cell lymphoma; Human immunodeficiency virus; R-DHAP; R-CHOP

Core tip: There are limited reports related to successful management of primary hepatic lymphoma in human immunodeficiency virus (HIV) patients. This case report is not only considered as the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature, but also describes the use of R-DHAP as an induction regimen in the setting of significant impaired liver function and severe immunocompromised status. The use of R-DHAP as an induction regimen in management of primary hepatic lymphoma in HIV patients was never reported.

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INTRODUCTION

Primary hepatic lymphoma (PHL) is a rare disease associated with immunodeficiency diseases and chronic viral hepatitis. From 1981 to 2003, only 358 cases of primary hepatic lymphoma were reported[1]. Data surrounding disease managements in patients with human immunodeficiency virus (HIV) infection is lacking. Here, we present a case of an HIV positive man whose PHL subsided into complete remission after chemotherapy.

CASE REPORT

A 32-year-old man with no known significant chronic medical problems was admitted to the hospital due to severe right upper quadrant abdominal pain, fever, night sweats, and unintentional weight loss. There was no history of recent heavy alcohol consumption. The patient appeared jaundiced and had a tender and firm hepatomegaly with a liver span of 19 cm. The lymph node was not enlarged. An abdominal ultrasound revealed multiple small hypoechoic lesions throughout the liver, common bile duct of 3.2 mm and normal gallbladder without gallstones. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed hepatomegaly with multiple small low attenuation nodules throughout the liver parenchyma, normal common bile duct and small ascites in the pelvis (Figure 1). Magnetic resonance imaging of the abdomen with intravenous contrast confirmed CT scan findings. All imaging studies showed no extrahepatic lymphadenopathies. A liver biopsy of lesions revealed diffuse large B cell lymphoma with non-specific lobular hepatitis (Figure 2). Immunohistochemical stains of the liver specimen revealed $CD20^+$, $CD79^+$, $CD79a^+$, $CD4^-$, and $CD3^-$ cells (Figure 3). The patient also tested positive for HIV infection. Tests for hepatitis B and C were negative. Additional tests results are shown in Table 1.

The patient was diagnosed with Stage 1BE primary liver large B cell lymphoma, and started on anti retroviral therapy along with chemotherapy during in-patient care. The initial anti retroviral medications were efavirenz, emtricitabine, and tenofovir. On the 7th day of the treatment, efavirenz was changed to raltegravir due to the presence of G190A mutation on HIV genotyping testing which confers resistance to non-nucleoside reverse transcriptase inhibitor mutation. Eight cycles of chemotherapy were administered together with anti retroviral therapy. In view of elevated liver enzymes and jaundice, chemotherapy with a platinum based regimen (R-DHAP) was initiated. The regimen of this first cycle consisted of 1.5 mg/kg of oral prednisone, 375 mg/m^2 of rituximab, 100 mg/m^2 of cisplatin, and 2000 mg/m^2 of cytarabine. As the co-administration of cisplatin and tenofovir might have increased his risk of toxicity to the kidney proximal tubule, serum creatinine was monitored closely. His serum creatinine levels were always less than 1 mg/dL and the calculated creatinine clearance was maintained at the level of 77 mL/min per 1.73 m^2. Nine days after starting the first chemotherapy cycle, he developed significant thrombocytopenia (nadir of 10000 cells/uL) and neutropenia (nadir of 300/uL). When platelet count was 10000/uL, the patient had an episode of epistaxis which was controlled after platelets transfusion. He did not develop fever during the episode of neutropenia. Filgrastim was given for 3 d when neutropenia was 300/uL. Upon the completion of first cycle of chemotherapy, the patient remained afebrile and became less jaundiced. Chemotherapy normalized liver enzymes and bilirubin (Table 1). Next, a CHOP regimen containing cyclophosphamide (600 mg/m^2), adriamycin (50 mg/m^2), vincristine (1.1 mg/m^2), and prednisone was administered. Rituximab (375 mg/m^2) was added to the CHOP regimen to start a third cycle of chemotherapy administered every 3 wk. As there was no known significant drug-drug interaction between the R-CHOP regimen and the anti retroviral regimen (tenofovir, emtricitabine and raltegravir), all medications were given according to the standard doses. After the second cycle, the patient remained anicteric with a body weight improvement of 5 kg from baseline. A CT with positron emission tomography (PET) scan performed after the 4th cycle of chemotherapy showed that the liver had reduced in size from 19.5 cm (prior to treatment) to 16.5 cm without evidence of hypermetabolic foci in the neck, chest, abdomen, or pelvis. Re-staging images with CT-PET after the 6th cycle revealed normal uptake within liver, spleen, adrenal glands, renal cortices, and the collecting system. A CT-PET scan at 5 and 11 mo after the last cycle confirmed remission (Figure 4). He is still in remission 19 mo after the treatment. During the chemotherapy, the CD4 count had improved and HIV viral loads were always undetectable (Table 1).

DISCUSSION

Fifty thousand incident cases of lymphoid neoplasms and 19000 related deaths occurred in the United States in 2005[2]. Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma subtype and accounts for approximately 23% of all cases[3]. Chronic hepatitis C and hepatitis B and autoimmune diseases increase the risk of PHL[4,5]. Although the liver contains lymphoid tissue and is an important site for lymphocytes activation[6], PHL is rare. Host factors make the liver a poor environment for malignant lymphoma development[4,7].

Table 1 Laboratory tests prior to the chemotherapy cycles and six months post chemotherapy

	Prior to the 1st	Prior to the 2nd	Prior to the 3rd	Prior to the 4th	Prior to the 5th	Prior to the 6th	Prior to the 7th	Prior to the 8th	6 mo post chemotherapy
Hgb (g/dL)	11.9	11.3	11.1	11.3	12	12.5	11.8	12.3	14.6
Platelet count (× 10^3 /uL)	107	95	107	34	169	132	60	78	70
WBC (× 10^3/uL)	5.9	10.6	1.9	11.9	3.7	4.1	3.3	3.5	5.9
Serum albumin (g/dL)	3.5	4.5	4.4	4.5	4.5	4.5	4.6	4.1	4.9
Serum AST (unit/L)	529	38	26	26	31	23	31	26	24
Serum ALT (unit/L)	270	43	37	30	28	27	39	31	30
Serum alkaline phosphatase (unit/L)	1686	442	146	210	1025	1586	1454	190	117
Serum GGT (unit/L)	872	-	-	-	-	149	-	-	-
Serum LDH (unit/L)	1838	313	-	331	326	263	-	148	124
Total bilirubin (mg/dL)	9.7	0.9	0.6	0.5	0.2	0.2	0.4	0.3	0.7
CD4 lymphocyte count (/mm^3)	155	651	-	265	-	-	173	-	729
HIV viral load (copies/mL)	485127	81	-	< 75	-	-	< 75	-	< 75

HIV: Human immunodeficiency virus.

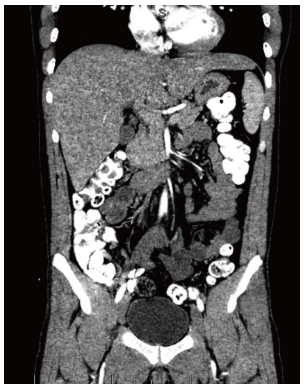

Figure 1 Computed tomography abdomen and pelvis prior to chemotherapy showing multiple small low attenuation nodules throughout the entire liver parenchyma.

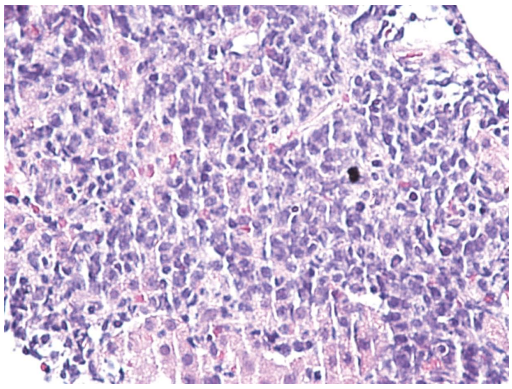

Figure 2 Liver biopsy showing diffuse large B-cell lymphomatous infiltrate.

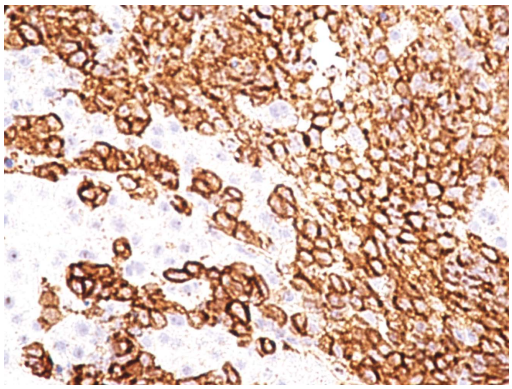

Figure 3 Immunohistochemical stain of liver specimen showing the lymphoma cells are strongly immunoreactive to CD 20.

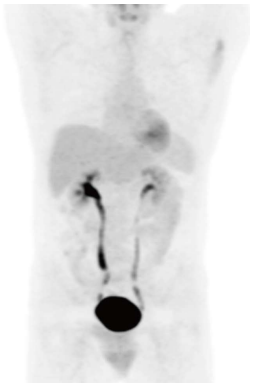

Figure 4 Maximum intensity projection of positron emission tomography/computed tomography scan at 11 mo after the last cycle of chemotherapy showing no hypermetabolic lesions in the liver.

Criteria for establishing the diagnosis of PHL include clinical, histopathological, and radiological findings. Lei *et al*[8] listed the following criteria to establish diagnosis: (1) signs and symptoms related to liver involvement at presentation including laboratory abnormalities and right upper quadrant mass or pain; (2) absence of both palpable adenopathy at presentation and radiologically evident distant lymphadenopathy; and (3) absence of leukemia on a peripheral smear.

A report from Lei[9] showed that among 90 patients with PHL, the most frequent presenting symptoms were upper abdominal pain or discomfort (56%), weight loss (40%), and fever (22%), which

occasionally mimic pyogenic liver abscess. Other symptoms included fatigue (13%), nausea and vomiting (12%), anorexia (8%), night sweats (8%), hemorrhagic diathesis (2%), dysphagia (2%), and rarely, immune thrombocytopenic purpura (1%) and hepatic encephalopathy (1%). In this particular report, 10% of patients were diagnosed incidentally without preceding symptoms. Physical examinations frequently revealed a modest hepatomegaly (82%), but jaundice infrequently presented only as a late manifestation of disease progression or related to underlying cirrhosis (13%)[9]. Lactate dehydrogenase and alkaline phosphatase are sometimes elevated[10]. Alpha-fetoprotein and carcinoembryonic antigen are often normal[4,10]. Radiologically, the presentation of multiple well-defined liver masses is more common than single lesions or diffuse hepatic involvement[11]. On ultrasound imaging, PHL is usually hypoechoic relative to a normal liver. CT scans of PHL usually show hypoattenuating lesions[4,11]. FDG-PET studies are extremely useful in evaluating treatment responses in PHL[12]. Histologically, primary diffuse large B cell lymphoma shows demarcated tumors with no intrasinusoidal invasion, atrophic reactive lymph follicles, and tests positive for the following antigens: CD10, Bcl2, Bcl6, MUM1, and CD25[5].

The United States National Comprehensive Cancer Network recommends managing diffuse large B cell lymphoma with rituximab, cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP protocol)[13]. Other regimens include CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, high dose methotrexate alternating with ifosfamide, etoposide, high dose cytarabine with or without rituximab), dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), dose adjusted EPOCH with rituximab, CDE (cyclophosphosphamide, doxorubicin and etoposide), CDE with rituximab, and hyperCVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate, and cytarabine with or without rituximab)[13]. Serrano-Navarro *et al*[1] highlighted a patient with PHL who developed complete response to R-CHOP treatment regimen, remaining symptom free for more than two years. Others also reported complete response to R-CHOP in non-HIV infected patients with diffuse large B cell type primary hepatic lymphoma[14-17]. Besides the R-CHOP regimen, a regimen contains rituximab, dexamethasone, high dose cytarabine, and cisplatin (R-DHAP) has been used as a salvage therapy in patients with CD20+ diffuse large B cell lymphoma who develop first time relapse or failure with first line therapy[18]. In addition, R-DHAP, given as remission induction chemotherapy, improved progression free survival and failure free survival in patients with aggressive CD20+ non-Hodgkin lymphomas[19].

In an article in French literature, Walter *et al*[17] reported the only favorable response to an R-CHOP treatment regimen for diffuse large B cell type PHL in an HIV infected patient. The case report described a 34-year-old man whose abdomen CT scan showed multiple liver masses, the largest of which was 14 cm. After four cycles of R-CHOP treatment, the masses markedly regressed with only a residual 5 cm hypodense lesion. Our patient developed complete remission without residual hepatic lesions. To our knowledge, this is the first report of PHL treatment in an AIDS patient that resulted in a complete response. After initial treatment with an R-DHAP regimen, serum levels of liver enzymes and bilirubin, very important in preventing the prolonged half-life of cyclophosphamide and neurotoxicity of vincristine[20], decreased. This may have facilitated further remission from the R-CHOP regimen. Further studies in HIV positive patients may confirm these findings.

COMMENTS

Case characteristics

A 32-year-old man with recent history of unintentional weight loss presented with right upper quadrant pain.

Clinical diagnosis

Patient appeared jaundiced and had a tender and firm hepatomegaly with a liver span of 19 cm.

Differential diagnosis

Acute ascending cholangitis, alcoholic hepatitis and infiltrative liver disease.

Laboratory diagnosis

WBC 5.9 K/μL; ALT 270 unit/L; AST 529 unit/L; serum alkaline phosphatase 1686 unit/L; serum GGT 872 unit/L; serum total bilirubin 9.7 mg/dL; human immunodeficiency virus (HIV) viral load 485 K copies/mL.

Imaging diagnosis

Computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed hepatomegaly with multiple small low attenuation nodules throughout the liver parenchyma, normal common bile duct and small ascites in the pelvis. Magnetic resonance imaging confirmed CT scan findings.

Pathological diagnosis

A liver biopsy of lesions revealed diffuse large B cell lymphoma with non-specific lobular hepatitis. Immunohistochemical stains of the liver specimen revealed $CD20^+$, $CD79^+$, $CD79a^+$, $CD4^-$, and $CD3^-$ cells.

Treatment

Eight cycles of chemotherapy were administered. R-DHAP regimen was given in the first cycle. CHOP regimen was started in the second cycle. R-CHOP regimen was started in the third cycle.

Related reports

In view of elevated liver enzymes and jaundice, chemotherapy with a platinum based regimen (R-DHAP) was given in the first cycle of chemotherapy. Upon completion of the first cycle, the patient became less jaundiced.

Term explanation

Cluster of differentiation (CD) of immunohistochemical stain is referred to a group of antibodies recognizing an antigen. For example, the T-helper cell antigen is called CD4 antigen and the various antibodies reacting with this antigen are called CD4 antibodies.

Experiences and lessons

This case report is not only considered as the first report of complete remission of primary hepatic diffuse large B cell lymphoma in an HIV positive patient in the English literature, but also describes the use of R-DHAP as an induction regimen in the setting of significant impaired liver function and severe

immunocompromised status. The use of R-DHAP as an induction regimen in management of primary hepatic lymphoma in HIV patients was never been reported.

Peer review

This case report well written overall.

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